Please replace claims 1-11 with the clean version provided above.

The specification has been amended to insert the priority claim.

Claims 1 and 5 have been amended to more particularly point out and distinctly claim the invention. Support for this amendment is found throughout the specification, particularly at: page 16, lines 17-20; page 30, line 18 through page 32, line 6; page 38, lines 20 through page 39, line 3; Figure 11.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**."

No new matter has been added by any of the above amendments and new claims. Accordingly, their entry by the Examiner is respectfully requested.

Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

Priority

The Office Action has stated that the Applicants have not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. §119(e) in that the application does not contain a specific reference to the prior applications in the first sentence.

The Applicants have amended the specification to include the necessary cross-reference to related applications.

Rejection under 35 U.S.C. §112, first paragraph

Claims 1-11 have been rejected under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The Office Action asserts that, although the Applicants have elected the species of antibodies, neither the claims nor the specification distinctly and specifically point out the identity of

any antibodies suitable for use as an agent in practicing the claimed invention and that one of skill in the art cannot predict which antibodies will suitably provide efficacy in the claimed invention. The Office Action further claims that all of the therapeutic agents listed in the specification would have been contemplated for use by one of skill in the art and, thus, there is no apparent contribution to the art in regard to the specific agent that is to be used in practicing the claimed invention. The Office Action also asserts that it cannot be predicted by one of skill in the art that such an agent actually exists or could be created because the specification lacks exemplification of the claimed method and of specific teachings that would enable one of skill in the art to practice the claimed invention.

The Applicants first point out that the present invention is based on the novel discovery that overexpression and accumulation of apoE causes hypertriglyceridemia by stimulating VLDL production and by impairing VLDL lipolysis. Thus, it necessarily follows that reducing the plasma level of active apoE will also reduce the plasma level of VLDL. The claims have been amended to reflect this novel cause-and-effect relationship by specifying that the amount of active apoE is reduced by an amount sufficient to reduce VLDL production.

The Applicants respectfully submit that one of skill in the art would recognize that they had possession of the claimed invention at the time the application was filed. A detailed list of many agents suitable for use in the present invention is found in the specification at, for example, page 10, line 1 through page 16, line 16. Such agents include naturally occurring or synthetic small molecule compounds, antibodies or fragments thereof, antisense molecules, and catalytic nucleic acid compounds. In addition, the Applicants have disclosed methods of screening agents for effectiveness, and have even provided animal models, in the specification at, for example, page 23, line 11 through page 26, line 26, and throughout the Experimental section. Such disclosure includes methods for detecting and quantifying apoE, VLDL, and triglycerides. Thus, many different agents are described in the specification and the specification also provides a method for screening agents for their ability to at least reduce the amount of plasma active apoE.

The Office Action also asserts that the specification has not pointed out any antibodies for use in the invention; however, this claim is incorrect. The specification does describe specific antibodies of interest on page 14, lines 6-11. Furthermore, by citing Huff *et al.* (Arterioscler. Thromb. (1991) 11:221-233) in the §103 rejection, the Office Action has shown that other antibodies to apoE are known in the art. The Applicants note that it is well-established that a "patent need not teach, and preferably omits,

what is well known in the art." MPEP §2164.01. Thus, the disclosure of antibodies in the specification, coupled with the additional anti-apoE antibodies which are known in the art, is sufficient.

Furthermore, contrary to the assertion made in the Office Action, there is a contribution to the art regarding the specific agent to be used in practicing the claimed invention. While the broad classes of different types of agents disclosed in the specification might have generally been known to the skilled artisan, that artisan would *not* have known to look within these broad classes for agents which reduce apoE and would *not* have known to use these agents to reduce VLDL production by reducing active apoE because, until the Applicants' invention, the effect of apoE on such production was not known. Thus, the Applicants have made a definite contribution to the art by identifying this novel cause-and-effect relationship and, based on this disclosure, one of skill in the art could readily screen for agents which have the desired effect.

The Office Action also asserts that it cannot be predicted by one of skill in the art that such an agent actually exists or could be created because the specification lacks exemplification of the claimed method and of specific teachings that would enable one of skill in the art to practice the claimed invention. Applicants disagree with this assertion and point out that agents which directly effect apoE are already known in the art. For example, Huff *et al.* describes an anti-apoE monoclonal antibody which is known to bind to apoE and block the binding of apoE to the LDL receptor (See abstract). In addition, as noted above, the specification describes other antibodies to apoE and, since the amino acid sequence of apoE is known, production of additional antibodies would be routine for the skilled artisan. Furthermore, the nucleotide sequence of apoE is known so one of skill in the art would also fully expect to be able to use antisense technology to reduce apoE expression. Finally, Lucas *et al.* (J. Biol. Chem. (1997) 272:13000-5 (abstract enclosed)) describes a reduction in monocyte-derived macrophage secretion of apoE by addition of LPL. Thus, several known methods of reduction of apoE are at the disposal of the skilled artisan to practice the claimed invention and the artisan would fully expect to identify other suitable agents based on the specification and that which is known in the art.

All that is necessary to fulfill the written description requirement is that one of skill in the art recognize that the Applicants invented what is claimed. MPEP §2163.02. The Applicants have disclosed the novel discovery that overexpression and accumulation of apoE causes hypertriglyceridemia by stimulating VLDL production and by impairing VLDL lipolysis, have provided a detailed list of many agents suitable for use in the present invention, have provided references containing specific antibodies of interest, and have provided methods and animal models for determining which agents are useful in the claimed methods. Their discovery, coupled with the

disclosure in the specification and that which is known in the art, would convey to the skilled artisan that the Applicants were in possession of the claimed invention. Accordingly, the Applicants respectfully request that this rejection of Claims 1-11 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claims 1, 3-8, 10, and 11 have been rejected under 35 U.S.C. §112, first paragraph, for the asserted reason that they contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which they pertain, or with which they are most nearly connected, to make and/or use the invention. The Office Action states that "the specification cannot be extrapolated to the enablement of the claims because the specification provides insufficient guidance and exemplification of the use of the claimed method to effectively reduce the plasma level of triglyceride and at least one VLDL in the plasma of a mammal and to thereby treat hyperlipidemia in said mammal." Paper No. 9, page 10. The Office Action also asserts that the specification does not exemplify the method, provide a teaching that such an agent actually exists, provide guidance as to how apoE3 patients are to be selected, or teach how the efficacy of the method of treatment can be measured or determined.

The law is clear that "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." United States v. Telectronics, Inc., 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), cert. denied, 490 U.S. 1046 (1989). See also, Genentech, Inc. v. Novo Nordisk, 42 USPQ 2d 1001 (Fed. Cir. 1997), cert. denied, 522 U.S. 963 (1997); Scripps Clinic and Research Foundation v. Genentech, Inc., 18 USPQ 2d 1001 (Fed. Cir. 1991). Furthermore, the courts have taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia, 227 USPQ 428 (Fed. Cir. 1985). See also, MPEP §2164.01. Practitioners in the chemical and molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the molecular biology arts. For example, in Hybritech v. Monoclonal Antibodies, Inc. (231 USPQ 81 (Fed. Cir. 1986)) the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art which routinely performs such long experiments. Thus,

the test of enablement is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine.

As amended, the claims are directed to a method for reducing the plasma level of VLDL in a host, and a method of treating a host suffering from a disease condition associated with elevated plasma level of VLDL, by administering to the host an effective amount of an agent which at least reduces the amount of plasma active apoE in the host by an amount sufficient to reduce VLDL production. The Applicants respectfully submit that the specification and the amended claims, coupled with the information known in the art, would enable one of skill in the art to use the invention without undue experimentation.

One of skill in the art of using agents to obtain a desired result in a host routinely performs screening of agents to identify those that are effective in achieving the desired result and to determine appropriate dosage and route of administration. The Office Action cites Gura (Science (1997) 278:1041-1042) to support the contention that it is well known that the art of drug discovery for therapy is highly unpredictable. Rather, the Applicants submit that this reference actually demonstrates that one of skill in the art of such therapy is accustomed to performing extensive screening experiments and that such experiments are no more than routine to the skilled artisan. In addition, the Applicants have provided a detailed list of many agents suitable for use in the present invention at, for example, page 10, line 1 through page 16, line 16. Such agents include naturally occurring or synthetic small molecule compounds, antibodies or fragments thereof, antisense molecules, and catalytic nucleic acid compounds. Included in the disclosure of agents for use in the invention are two references which provide specific antibodies of interest. See page 14, lines 6-11. Furthermore, in the Experimental section, additional antibodies specific for apoE were used in several of the experiments (See, e.g., page 29, lines 5-7) and the Huff, *et al.* reference (Arterioscler. Thromb. (1991) 11:221-233) cited in the Office Action also discloses an antibody known to bind to apoE. Finally, as noted above, other methods for reducing the amount of plasma active apoE are already known in the art.

In addition, the Applicants have disclosed methods of screening agents for effectiveness, and have even provided animal models, in the specification at, for example, page 23, line 11 through page 26, line 26, and throughout the Experimental section. Such disclosure includes methods for detecting and quantifying apoE, VLDL, and triglycerides. Thus, the specification provides the skilled artisan with all that is needed to identify agents for use in the methods of the present invention without any more experimentation than is routine in the art.

Thus, many different potential agents are described in the specification and some additional potential agents are known in the art. Furthermore, the specification provides methods of screening for agents useful in the methods of the present invention. What was not known until the Applicants'

discovery was that overexpression and accumulation of apoE actually *causes* hypertriglyceridemia by stimulating VLDL production and by impairing VLDL lipolysis. Since the specification, coupled with that which is known in the art, would enable the skilled artisan to practice the subject invention without undue experimentation, the Applicants respectfully request that this rejection of Claims 1, 3-8, 10, and 11 have been rejected under 35 U.S.C. §112, first paragraph, be withdrawn.

Rejection under 35 U.S.C. §112, second paragraph

Claims 1-11 have been rejected under 35 U.S.C. §112, second paragraph, as assertedly indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as their invention. The Office Action contends that claims 1 and 5 are indefinite because there is no positive process step that clearly relates back to the preamble of the claims.

This rejection is obviated by the amendment to claim 1 to insert the phrase "to reduce the plasma level of VLDL in said host" and the amendment to claim 5 to insert the phrase "to reduce VLDL production to treat said disease condition."

Rejection under 35 U.S.C. §102

Claims 1-11 have been rejected under 35 U.S.C. §102(b) as allegedly anticipated by Ditschuneit *et al.* (J. Med. Res. (1992) 20:197-210), as evidenced by Pedreno *et al.* (Metabolism (2000) 49:942-949) and Durrington *et al.* (Atherosclerosis (1998) 138:217-225). The Office Action asserts that Ditschuneit *et al.* teaches a method of treating female patients with hyperlipoproteinaemia type IV with gemfibrozil and that the mechanism by which an agent acts to treat a disease is an inherent property of that agent. The Office Action then points to Pedreno *et al.* and Durrington *et al.*, claiming that they teach that gemfibrozil causes a reduction in levels of triglyceride, VLDL and apoE in a patient.

As noted above, the presently pending claims have been amended to reflect the novel discovery that apoE affects VLDL production. Nothing in the cited references teach that apoE is a target for reducing levels of VLDL production. In fact, the mechanism of action of gemfibrozil, a fibric acid derivative, is thought to be through stabilization of LDL receptor mRNA (Goto *et al.* (1997) Arterioscler. Thromb. Vasc. Biol. 17:2707-12 (abstract enclosed)), not through reducing the amount of active apoE. Not until the Applicants made their invention was it known that apoE had an effect on VLDL production; however, the Office Action maintains that gemfibrozil inherently anticipates the present invention.

According to the law, a reference may anticipate a claim even if a feature recited in the claim is not specifically disclosed in the reference. However, the law is established that where the reference is silent as to a specific limitation in the claims, such a gap in the reference must be filled with recourse to extrinsic evidence in order for the reference to serve as an anticipatory reference by inherency. Such evidence must make clear that the missing descriptive matter is *necessarily* present in the thing described in the reference, *and that it would be so recognized by persons of ordinary skill in the art* at the time the invention was made. Continental Can Co. USA, Inc. v. Monsanto Co., 20 USPQ 2d 1746, 1749-1750 (Fed. Cir. 1991). The characteristic must flow *undeniably and irrefutably* from the express disclosures of the prior art reference. Mere possibilities or even probabilities are not enough to support a finding of anticipation. Motorola, Inc. v. Interdigital Technology Corp., 43 USPQ 2d 1481 (Fed. Cir. 1997). In relying upon a theory of inherency, the Office Action must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art. Ex parte Levy, 17 USPQ 2d 1461, 1464 (Bd.Pat.App.& Inf. 1990).

Nothing in either Pedreno *et al.* or Durrington *et al.* provides the showing required by law to support the rejection based on the alleged inherent property of gemfibrozil. In fact, the common knowledge in the art, as evidenced by the abstract mentioned above, is that the mechanism of action of gemfibrozil is through increasing LDL receptor expression, for which apoE is a ligand. Since apoE is a component of VLDL, an increase in LDL receptor will result in enhance clearance of plasma VLDL (see Huang *et al.*, page 26388, right column). Further, because apoE is a component of the VLDL particles, apoE levels will also be reduced when VLDL clearance is increased; however, this decrease in apoE is not a direct effect of the agent as the claims require.

Thus, the claimed invention and the mechanism of gemfibrozil are not the same. Accordingly, Ditschuneit *et al.*, as evidenced by Pedreno *et al.* and Durrington *et al.*, does not anticipate Claims 1-11 and this rejection under 35 U.S.C. §102(b) should be withdrawn.

Claims 1, 3-8, and 10-11 have been rejected under 35 U.S.C. §102(b) as allegedly anticipated by Yoshino *et al.* (Atherosclerosis (1989) 75:67-72). The Office Action asserts that Yoshino *et al.* teaches that treating patients with pravastatin results in a significant decrease in the levels of triglyceride, VLDL, and apoE in the plasma of the patients.

As pointed out above, the presently pending claims have been amended to reflect the novel discovery that reducing apoE *causes* a reduction in VLDL production. Nothing in the cited reference teaches that apoE is a target for reducing VLDL production. As discussed above for gemfibrozil, there is no evidence that pravastatin acts to decrease VLDL production by reducing active apoE, while there is evidence that it acts through a different mechanism in that it is a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This inhibition of HMG-CoA reductase leads to upregulation of the LDL receptor, which, in turn, leads to enhanced clearance of plasma VLDL. Since apoE is a component of the VLDL particles, apoE levels will also be reduced when VLDL is cleared; however, this decrease in apoE is not a direct effect of the agent as the claims require. In addition, if pravastatin decreased VLDL production by decreasing apoE, one of skill in the art would expect that it would have other effects opposite to that of an overexpression of apoE, but it does not. Huang *et al.* (J. Biol. Chem. (1998) 273:26388-26393) state:

> ...apoE is a ligand for the LDL receptor, cell-surface heparan sulfate proteoglycans, and the LDL receptor-related protein. Thus, apoE accumulation in the VLDL would effectively mediate the clearance of the VLDL from plasma and, at the same time, impair lipolytic processing of the VLDL to LDL. The combined effect of apoE in VLDL clearance and lipolysis would result in decreased LDL. In fact, plasma LDL cholesterol levels in [hypertriglyceridemia] patients are normal or slightly decreased.

Page 26393. Thus, increased apoE results in normal or decreased LDL levels; however, Yoshino *et al.* show a significant decrease in LDL cholesterol levels after 6 months of treatment with pravastatin and a further decrease by the 12th month of treatment (page 68, right column, last full paragraph). This is the opposite effect on LDL cholesterol that would be expected if pravastatin decreased VLDL production by decreasing active apoE, and would lead one of skill in the art to believe that the mechanism of action is not through apoE.

Thus, there is nothing in Yoshino *et al.* to suggest that pravastatin decreases VLDL production by reducing active apoE. Accordingly, this rejection of Claims 1, 3-8, and 10-11 under 35 U.S.C. §102(b) should be withdrawn.

Claims 1, 3-8, and 10-11 have been rejected under 35 U.S.C. §102(b) as allegedly anticipated by Connor *et al.* (Ann. NY Acad. Sci. (1993) 683:16-34). The Office Action contends that Connor *et al.* teach dramatic reduction in plasma triglycerides resulting from treatment with dietary n-3 fatty acids, as well as a decrease in the levels of VLDL and apoE.

Nothing in the cited reference teaches that apoE is a target for reducing levels of VLDL production or that reduction of active apoE will cause a reduction in VLDL production. Furthermore, there is nothing that suggests that n-3 fatty acids act to decrease VLDL production by reducing active apoE, while there is evidence that n-3 fatty acids act through a different mechanism. As noted above, if the cited agent decreased VLDL production by decreasing apoE, one of skill in the art would expect that it would have other effects opposite to that of an overexpression of apoE. Huang *et al.* teaches that increased apoE results in normal or decreased LDL levels; however, Connor *et al.* states that dietary n-3 fatty acids caused a reduction in LDL. This is the opposite effect on LDL level that would be expected if n-3 fatty acids acted by decreasing active apoE and would lead one of skill in the art to believe that the mechanism of action is not through apoE.

Thus, there is nothing in Connor *et al.* to suggest that dietary n-3 fatty acids decrease VLDL production by reducing active apoE. Accordingly, this rejection of Claims 1, 3-8, and 10-11 under 35 U.S.C. §102(b) should be withdrawn.

Rejection under 35 U.S.C. §103

Claims 1, 2, 4-9, and 11 have been rejected under 35 U.S.C. §103(a) as allegedly obvious over Huff *et al.* (Arterioscler. Thromb. (1991) 11:221-233) in view of Huang *et al.* (J. Biol. Chem. (1998) 273:26388-26393). The Office Action contends that Huff *et al.* teaches an anti-apoE monoclonal antibody known to block the binding of apoE to the LDL receptor and suggests that apoE mediates the accumulation of cholesterol in macrophages incubated in the presence of VLDL isolated from patients with type IV hyperlipoproteinaemia. The Office Action also notes that Huff *et al.* does not teach a method of reducing the plasma level of at least one of VLDL and triglycerides in a host nor a method of treating a host suffering from a disease condition associated with elevated levels of at least one of VLDL and triglycerides. The Office Action then contends that it would have been obvious to one of ordinary skill in the art to use the anti-apoE antibody of Huff *et al.* to treat patients since Huang *et al.* teaches that overexpression and accumulation of apoE causes hypertriglyceridemia and that animals with the disease have elevated serum levels of VLDL and triglyceride.

In order for a reference to form the basis of a §103 rejection, it must be available as prior art under §102 (See MPEP §2141.01). Since Huang *et al.* was published less than one year prior to the filing date of the present application, the only portion of §102 under which Huang *et al.* could potentially be prior art is subsection (a); however, the Applicants respectfully submit that Huang *et al.*

does not meet the requirements of 35 U.S.C. §102(a) as a reference (See In re Katz, 215 USPQ 14 (CCPA 1982)). Section 102(a) reads: "A person shall be entitled to a patent unless (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent."

A printed publication cannot stand as a reference under §102(a) unless it describes the work of another. A prior patent or printed publication is not "prior art" if the disclosure is that of the Applicants' own work, until the end of the one year period afforded under §102(b), during which time an inventor is allowed to perfect, develop and apply for a patent on his invention and publish descriptions of it if he wishes.

Since the publication in this case occurred less than one year before the Applicants' application, the disclosure comes within the scope of §102(a) only if the description is not of the Applicants' own work. Authorship of an article by itself does not raise a presumption of inventorship with respect to the subject matter disclosed in the article. Thus, co-authors may not be presumed to be coinventors merely from the fact of co-authorship.

Applicants have provided a Declaration made under 35 U.S.C. §1.132 describing the contributions of the co-authors Xiao Qin Liu, Dr. Stanley C. Rall, Jr., Dr. Arnold von Eckardstein, and Dr. Gerd Assmann. The contributions of these four co-authors represented technical assistance, informational assistance, and assistance with obtaining materials for the study. Thus, the Applicants' explanation of the co-authors contribution is consistent with the content of the article and the nature of the publication, and it is clear that these co-authors did not make an inventive contribution to the present patent application.

Thus, Huang *et al.* describes the Applicants' own invention and cannot be used as prior art against the present application. Huff *et al.* does nothing more than describe a monoclonal antibody specific for apoE. It does not teach or suggest the methods of the present invention and cannot stand on its own in a rejection of the pending claims. Accordingly, in view of the above remarks and attached Declaration, the Applicants respectfully submit that the presently claimed invention is not obvious over Huff *et al.* in view of Huang *et al.* As such, the Applicants respectfully request withdrawal of this rejection of Claims 1, 2, 4-9, and 11 under 35 U.S.C. §103(a).

CONCLUSION

In view of the above remarks, this application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue.

If the Examiner finds that a Telephone Conference would expedite prosecution of this application, he is invited to contact the undersigned (650) 327-3400.

In the event that the transmittal letter is separated from this document and the Patent Office determines that extensions or other relief is required and/or fees are due applicants, the Applicant petitions for any required relief, including extensions of time, and authorize the Commissioner to charge our Deposit Account No. 50-0815, Order Number 6510-121US1, for any fees due in connection with the filing of this document. The Patent Office is not authorized to charge issue fees to our Deposit Account.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 4.30.01

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Enclosures:

- Lucas *et al.* (1997) *J. Biol. Chem.* 272:13000-5 (abstract)
- Goto *et al.* (1997) *Arterioscler. Thromb. Vasc. Biol.* 17:2707-12 (abstract)
- Huff *et al.* (1991) *Arterioscler. Thromb.* 11:221-33 (abstract)
- Declaration of Yadong Huang under 37 C.F.R. § 1.132

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

After line 2 on page 1, the following two paragraphs have been inserted:

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial No. 60/128,853, filed April 12, 1999, now abandoned, which application is incorporated herein by reference.

IN THE CLAIMS:

Claims 1 and 5 have been amended as follows:

1. (Amended) A method for reducing the plasma level of [at least one of] VLDL [and triglycerides] in a host, said method comprising:

administering to said host an effective amount of an agent which at least reduces the amount of plasma active apoE in said host by an amount sufficient to reduce VLDL production in said host to reduce the plasma level of VLDL in said host.

5. (Amended) A method of treating a host suffering from a disease condition associated with elevated plasma levels of [at least one of] VLDL [and triglycerides], said method comprising:

administering to said host an effective amount of an agent that at least reduces the plasma amount of active apoE in said host by an amount sufficient to reduce VLDL production to treat said disease condition.